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Mark A. Beno, Jack M. Williams*

Chemistry Division, Argonne National Laboratory Argonne, Illinois 60439

M. Tachikawa, E. L. Muetterties*

Department of Chemistry, University of California Berkeley, California 94720 Received March 7, 1980

Applications of Bridgehead Alkenes to Organic Synthesis. Regio- and Stereochemical **Control in the Diels-Alder Route to Polyfunctional** Cyclohexenes and Cyclohexanes

Sir:

Suitably functionalized bicyclic molecules occupy an important role in synthetic organic chemistry. The well-defined stereochemical relationship of the carbon framework permits simultaneous control over the relative configuration of a number of asymmetric centers. The stereochemical information contained in these bicyclic molecules can be retrieved in a subsequent fragmentation or cleavage reaction.

We report herein an application of this methodology to control stereo- and regiochemistry in the synthesis of polysubstituted cyclohexenes and cyclohexanes.

Our approach is outlined in Scheme I. A key step in the synthesis is an intramolecular Diels-Alder reaction that results in formation of a medium-ring bicyclic lactone containing a bridgehead double bond.¹ We illustrate, for the first time, the utility of bridgehead alkanes in organic synthesis by the ad-







dition-cleavage sequence shown in steps 2 and 3 in Scheme I. The addition step establishes the relative configuration of three asymmetric centers; cleavage of the original linkage between diene and dienophile results in formation of a di-, tri-, or tetrasubstituted cyclohexane with control over all asymmetric centers.

The specific compounds used to illustrate this sequence are the triene esters 2-4, chosen because of the ease of cleavage of the lactone bridge and the activating influence of the carbonyl group in the intramolecular Diels-Alder step.^{2,3}

Esterification of dienols 1a⁴ and 1b⁵ by the methods outlined in Scheme II results in 40-60% yields of triene esters 2-4.6 Intramolecular cycloaddition was accomplished by heating 0.1 M solutions in xylene. Cycloadditions were complete in 5-6 h. Typical reaction conditions: 185 °C for 2a, 2b, and 4a, and 130 °C for 3a and 3b. The bridgehead alkenes (5-7), formed in 40-60% yield, are sufficiently stable to allow isolation by

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Scheme III $CH_{3}O_{2}C$ + $CO_{2}CH_{3}$ $HO(CH_{2})_{3}OH$ $I_{4a}(58\%)$ + $I_{2}O(42\%)$ $H_{2}/P1O$ $HO_{-(CH_{2})_{2}OH}$ + $HO_{-(CH_{2})_{2}OH}$ $HO_{-(CH_{2})_{2}OH}$ + $HO_{-(CH_{2})_{2}OH}$ IOH

concentration under reduced pressure followed by chromatographic workup. Structure confirmation was obtained by a combination of spectroscopy⁶ and chemical correlation with the cycloadducts obtained from the bimolecular Diels-Alder reaction. For example, the product from cycloaddition of **2a**, bridgehead lactone **5a**, when treated with methoxide (NaOMe, HOMe, 0 °C, 1 min) produces a single cyclohexene derivative **8a**; this isomer corresponds to the minor component from the bimolecular Diels-Alder reaction between dienol **1a** and methyl acrylate (eq 1).⁷ (Compounds **8a** and **17** are only partially separated by capillary VPC.)

$$H = CHCO_2Me$$

$$H = CHCO_2Me$$

$$H = CO_2Me$$

Similarly, triene esters **3a** and **4a** afford a single adduct. This is consistent with our previous finding demonstrating regiospecificity when there are as many as five atoms in the bridge joining dienophile and diene.^{3,8} Indeed, regiospecificity is still high (>92%) with six atoms in the bridge. For example, cycloaddition of triene ester **2b** gave a mixture of cycloadducts, **5b** and **18**, in a ratio of 92:8. The minor component was separated chromatographically and characterized both spectroscopically⁶ and by correlation with the *major* component of the bimolecular Diels-Alder reaction (**19**), eq 2.

$$2b \longrightarrow 5b + 6c = 0 + 100$$

Thus, at least within the limited series studied, the intramolecular route offers a novel approach to the regiochemistry problem of 2-substituted dienes.⁹

These results also establish that the cycloadditions are stereospecific at the dienophile; trans- and cis-triene esters **3a** and **4a** result in formation of exo and endo bicyclolactones **6a** and **7a**, respectively. Our efforts to extend the series to bridgehead lactones containing four atoms in the lactone bridge have thus far been unsuccessful; despite the fact that the resulting bridgehead compounds would contain only a *trans*-cyclononene ring, the triene esters are reluctant to undergo cycloadditon.

Addition reactions to the carbon-carbon double bond of bridgehead alkenes occurs with almost complete syn stereo-selectivity; the bicyclic framework denies access of reagents to the back side of the molecule.¹⁰ The additon reaction fixes the relative configuration of three asymmetric centers; cleavage of the X-Y bridge unmasks the substituted cyclohexane.

Catalytic reduction of bridgehead lactones 5–7 affords a quantitative yield of bicyclic lactones 11, 12, and 13. Hydrolysis and esterification (CH_2N_2) gives the epimerically pure di- and trisubstituted cyclohexanes 14, 15, and 16. As expected, catalytic reduction of conformationally flexible cyclohexenes 8 and 9 gives isomeric mixtures (Scheme III).¹¹ Thus, reduction of 8a (obtained from cleavage of lactone 5a) results in a 58:42 mixture of cis- and trans-1,3-disubstituted cyclohexanes 14a and 20; reduction of 5a followed by hydrolysis and esterification yields pure *cis*-14a.

Utilization of the remaining asymmetric center is accomplished by the epoxidation-cleavage sequence illustrated in eq 3. Treatment of bridgehead alkene 5a with 1 equiv of m-



chloroperbenzoic acid yields bridgehead epoxylactone (21) (78%).⁶ Treatment of 21 with 1 equiv of sodium methoxide gives a single cyclohexane epoxide, 22. This isomer corresponds to one of the products obtained from epoxidation of cyclohexenol 8a (Scheme II).

The reactivity of the bridgehead double bond coupled with its high stereospecificity holds considerable promise for the application of bridgehead alkenes in organic synthesis. Work along these lines is underway.

Acknowledgment. Support for this research by the National Science Foundation Grant No. CHE-782g154 is gratefully acknowledged.

Supplementary Material Available: Spectroscopic properties of all new compounds (3 pages). Ordering information is given on any current masthead page.

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- (12) University of California Undergraduate President's Fellow

Kenneth J. Shea,* Philip S. Beauchamp, Ronald S. Lind¹² Department of Chemistry, University of California, Irvine Irvine, California 92717 Received June 11, 1979

Investigation of Crystalline Naphthazarin B by ¹³C NMR Spectroscopy Using "Magic Angle" Spinning Techniques and by X-ray Diffraction: Evidence for a Dynamic Disordered Structure

Sir:

Few organic molecules have been the subject of as many X-ray structural investigations as has naphthazarin.^{1,2} Several investigations of each of the three crystalline forms (designated A, B, and C) have led to the conclusion that in the crystalline state the molecule is centrosymmetric and, hence, can best be represented not as **1a** but as a resonance hybrid of structures such as **2a** and **2b**, i.e., the symmetrical form **2**.³



In contrast, solution studies such as dipole moment determination⁵ and NMR^{1,3,6} and IR⁷ spectroscopy have been interpreted in terms of structures **1a** and **1b** which are in rapid equilibrium on the NMR time scale down to -75 °C; an indirect argument has been made⁷ that an isolated molecule of the 1,5-quinone **3** should be very much less stable than **1a**. As a result, there appears to be acceptance of the belief that the molecular structure in the solid state (**2**) is different from that in solution (**1a** or **1b**) owing to the effect of crystal packing forces.^{1,7} The structure of naphthazarin is of interest not only in its own right, but because this assembly of functional groups occurs in clinically important antitumor antibiotics⁸ as well as in other natural products.^{1,2b}

It has recently been shown⁹ that, by a combination of high power proton decoupling, cross polarization,¹⁰ and "magic angle" spinning¹¹ techniques, it is possible to obtain relatively well-resolved high-resolution ¹³C NMR spectra of solid materials.¹² An important feature of these high-resolution ¹³C experiments in solids is that the chemical shift values obtained are the "isotropic" values for the solid state and may, therefore, be compared directly with those from solution NMR; these solid-state signals are averaged by chemical exchange processes in the same way as solution spectra¹³ and may thus be used to distinguish motions in the solid state which involve chemical exchange from those which do not.

In this communication we report the application of highresolution solid-state ¹³C NMR spectroscopy using these techniques and a further detailed X-ray structural study to this problem.

Interchange between the two tautomeric forms **1a** and **1b** involves primarily the movement of only two hydrogen atoms and might thus occur readily in the solid state; this process is accompanied by interchange between carbonyl and hydroxylic carbons which are both well resolved in the ¹³C NMR spectrum and easily assignable. Our new data strongly suggest that the structure of crystalline naphthazarin is dynamically disordered and involves a tautomeric equilibrium which is fast at room temperature (in the solid state).

The ¹³C NMR spectrum of a stationary sample of polycrystalline naphthazarin $B^{2,14}$ is shown in Figure 1A. Only broad, relatively featureless absorptions are observed, as would be expected since each of the carbons in the molecule should show a large shift anisotropy. The spectrum of the same sample recorded under identical conditions except that it is now also being spun rapidly (\sim 3.5 kHz) at the "magic angle" is shown in Figure 1B. Well-resolved ($\Delta V_{1/2} \simeq 25$ Hz) peaks are now observed in the spectrum. The fact that broad absorptions are observed for the stationary sample under the same experimental conditions rules out the possibility that the sharp absorptions in the MAS spectrum are due to very mobile, noncrystalline material or to some experimental artifact. Under a whole variety of experimental conditions only three peaks are observed in the spectrum, and no peak is observed at low field where the carbonyl groups would be expected to absorb, facts that are indicative of a fast chemical exchange process. This is confirmed by comparison of the solid-state spectrum (Figure 1B) with the high-resolution ¹³C spectrum from solution whose signals have been artificially line broadened (Figure 1C). The two spectra are identical, indicating that the same chemical exchange process is occurring in both phases. The peak assignments given in the caption to the figure are taken from the high-resolution solution spectrum¹⁵ and are confirmed by the different cross-polarization rates in the solid-state experiment where the four equivalent carbons which bear protons cross polarize much more efficiently than the other six.

When the temperature is lowered to -160 °C, there is a dramatic change in the spectrum (Figure 2). The highest field line assigned to carbons 9 and 10 is unchanged, and the other two absorptions each clearly split into two lines as would be expected for the freezing out of the dynamic exchange process.¹⁶

Dark-red prismatic crystals of the B form of naphthazarin from benzene or chloroform solution were examined by X-ray methods. Crystal data: $C_{10}H_{16}O$; mol wt, 190.2; monoclinic; a = 5.419 (1), b = 6.382 (2), c = 11.838 (3) Å; $\beta = 91.51$ (2)°; V = 409.3 Å³; Z = 2, space group $P2_1/c$. A total of 635 reflections was considered significantly above zero at the 2σ level out of a possible 699 within the Cu K α sphere ($2\theta \le 130^\circ$). Full-matrix refinement of a model with hydroxyl hydrogen